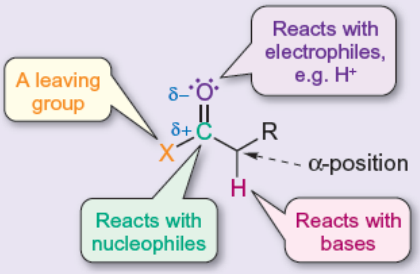
24

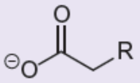
Carboxylic acids and derivatives: nucleophilic acyl substitution and α-substitution reactions

24.1 Structure and reactions of carboxylic acids and derivatives

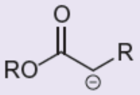
- Carboxylic acids and carboxylic acid derivatives (acyl chlorides, acid anhydrides, esters, and amides) have a C=O bond linked to an electronegative oxygen, nitrogen, or halogen atom.
- The C=O bond is polar and the electrons are attracted to the oxygen atom ($^{\delta+}C{=}O^{\delta-}$)—the oxygen atom reacts with electrophiles and the carbon atom reacts with nucleophiles.
- Deprotonation of a carboxylic acid (RCO_2H) forms a carboxylate ion (RCO_2^-), whereas deprotonation of an ester forms an ester enolate ion (H^+ is lost from the α-position).



X = OH (carboxylic acid); Cl (acyl chloride); OCOR (acid anhydride); OR (ester); NH_2, NHR, or NR_2 (amide)



A carboxylate ion



An ester enolate ion

- Carboxylic acids undergo a limited number of nucleophilic substitution reactions—many nucleophiles act as bases and deprotonate the carboxylic acid, rather than attack the C=O bond.
- Carboxylic acid derivatives undergo nucleophilic acyl substitution reactions, α-substitution reactions, and carbonyl-carbonyl condensation reactions.
- In a nucleophilic acyl substitution reaction the Cl, OCOR, OR, or NR_2 group bonded to C=O acts as the leaving group. (Aldehydes and ketones do not undergo nucleophilic acyl substitution reactions because the R and/or H groups bonded to C=O are very poor leaving groups.)
- The order of reactivity of carboxylic acid derivatives in nucleophilic acyl substitutions is: acyl chloride (RCOCl) > acid anhydride (RCO_2COR) > ester (RCO_2R) > amide ($RCONR_2$).
- The order of reactivity of carbonyl compounds towards nucleophiles is: acyl chloride (RCOCl) > acid anhydride (RCO_2COR) > aldehyde (RCHO) > ketone (RCOR) > ester (RCO_2R) > amide ($RCONR_2$).

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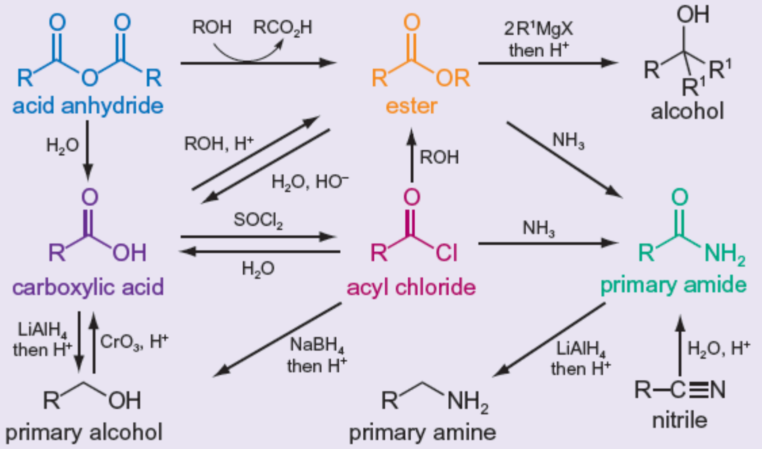
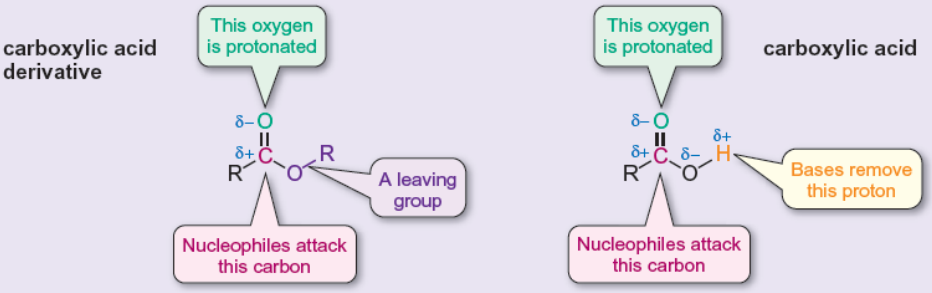
24.2 Nucleophilic acyl substitution reactions

- Acyl chlorides (RCOCl), acid anhydrides (RCO_2COR), esters (RCO_2R), and amides ($RCONH_2$, RCONHR, and $RCONR_2$) are called carboxylic acid derivatives because they can be prepared from a carboxylic acid (RCO_2H).
- Carboxylic acids and derivatives are useful compounds in synthesis because they can be converted into various functional groups. To convert one carboxylic acid derivative into another requires a nucleophilic acyl substitution reaction.



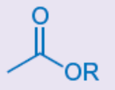
- Protonation of the C=O bond in a carboxylic acid or derivative converts it into a stronger electrophile, which reacts more rapidly with nucleophiles.



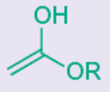
For practice questions on this topic, see questions 1–3 and 5 at the end of this chapter (pp.1134–1136).

24.3 α-Substitution and carbonyl–carbonyl condensation reactions

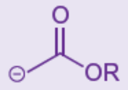
- For carboxylic acids and derivatives, the keto form is usually more stable than the enol form. The enol form and, particularly, the enolate ion are good nucleophiles that react with electrophiles in α-substitution reactions.



The **keto form** is generally the more stable

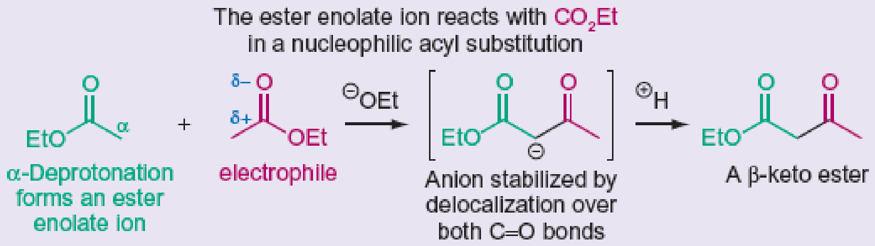


The enol form
(An enol form is stabilized by conjugation and intramolecular H-bonding)



An ester enolate ion is a strong nucleophile

- α-Bromination of carboxylic acids using a mixture of PBr_3 and Br_2 is called the Hell–Volhard–Zelinsky (HVZ) reaction.
- Reaction of two molecules of the *same* ester to form a β-keto ester is called a Claisen condensation.


The ester enolate ion reacts with CO_2Et in a nucleophilic acyl substitution

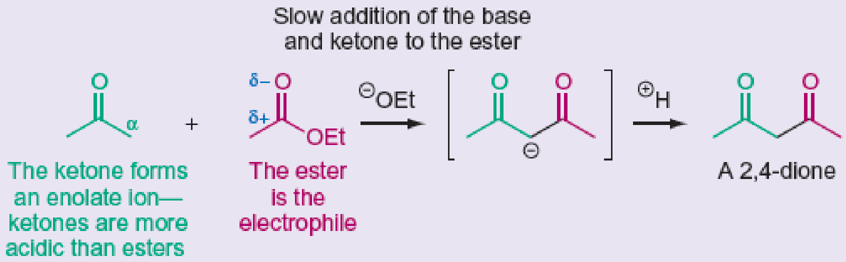
α-Deprotonation forms an ester enolate ion

electrophile

Anion stabilized by delocalization over both C=O bonds

A β-keto ester

- Reactions of two *different* ester molecules are called crossed (mixed) Claisen condensations.
- Related condensation reactions take place between an ester and an aldehyde or ketone.

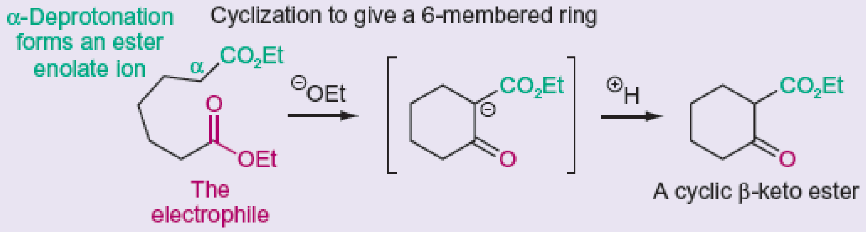

Slow addition of the base and ketone to the ester

The ketone forms an enolate ion—ketones are more acidic than esters

The ester is the electrophile

A 2,4-dione

- When a molecule containing two ester groups reacts with itself, this is called an intramolecular Claisen condensation or a Dieckmann reaction.


α-Deprotonation forms an ester enolate ion

Cyclization to give a 6-membered ring

The electrophile

A cyclic β-keto ester

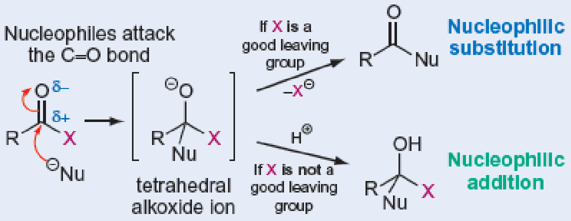
For practice questions on these topics, see questions 1, 2, 4, and 6 at the end of this chapter (pp.1134–1137).

Concept review

By the end of this chapter, you should be able to do the following.

- Recognize carboxylic acids, acyl chlorides, acid anhydrides, esters, and amides.
- Understand how carboxylic acids and derivatives react with nucleophiles, H^+, or a base.
- Draw a general mechanism for a nucleophilic acyl substitution reaction and explain why carboxylic acid derivatives react with nucleophiles in substitution reactions rather than addition reactions.

Nucleophilic substitution versus nucleophilic addition



- Explain why carboxylic acid derivatives are not equally reactive to nucleophiles.
- Draw general mechanisms for an α-substitution reaction and a carbonyl–carbonyl condensation reaction of a carboxylic acid derivative.
- Draw mechanisms for nucleophilic acyl substitution reactions of carboxylic acids (RCO_2H) using the following reagents: ROH, H^+ (catalyst); $SOCl_2$; NH_3 (heat).
- Draw mechanisms for nucleophilic acyl substitution reactions of acyl chlorides (RCOCl) using the following reagents: H_2O; ROH; $NaBH_4$ then H^+; NH_3 (two equivalents); RMgX (two equivalents) then H^+.
- Draw mechanisms for nucleophilic acyl substitution reactions of acid anhydrides (RCO_2COR) using the following reagents: H_2O; ROH; $LiAlH_4$ then H^+; NH_3 (two equivalents).
- Draw mechanisms for nucleophilic acyl substitution reactions of esters (RCO_2R) using the following reagents: H_2O, H^+; H_2O, HO^- then H^+; $LiAlH_4$ then H^+; NH_3; RMgX (two equivalents) then H^+.
- Draw mechanisms for nucleophilic acyl substitution reactions of amides (such as $RCONH_2$) using the following reagents: H_2O, H^+ (heat).
- Understand how nitriles (RCN) are hydrolysed to form carboxylic acids.
- Discuss keto–enol tautomerism in carboxylic acid derivatives and understand the factors that influence the stability of keto and enol forms.
- Draw the mechanism of α-bromination of a carboxylic acid using PBr_3 and Br_2.
- Explain why esters are less acidic than aldehydes or ketones.
- Draw mechanisms for Claisen condensations, crossed (mixed) Claisen condensations, and intramolecular Claisen condensations (Dieckmann reactions).
- Predict the structure of a product derived from a nucleophilic acyl substitution, an α-substitution, or a carbonyl–carbonyl condensation reaction of a carboxylic acid derivative.
- Propose reagents for converting a carboxylic acid derivative into a product derived from a nucleophilic acyl substitution, an α-substitution, or a carbonyl–carbonyl condensation reaction.